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(54) Title: A SYNERGISTIC PHARMACEUTICAL COMBINATION COMPRISING CICLETANINE FOR THE PREVENTION OR TREATMENT OF DIABETES

(57) Abstract: The invention refers to a synergistic pharmaceutical combination which comprises (a) a first pharmaceutical composition containing cicletanine or a pharmaceutically suitable acid addition salt thereof and one or more conventional carrier(s), and (b) a second pharmaceutical composition containing an antidiabetic or anti-hyperlipidemic active agent or, if desired and chemically possible, a pharmaceutically suitable acid addition salt or a salt formed with a pharmaceutically suitable base thereof and one or more conventional carrier(s). The pharmaceutical combination is suitable for the prevention or treatment of, among others, diabetes mellitus.

A SYNERGISTIC PHARMACEUTICAL COMBINATION COMPRISING CICLETANINE FOR THE PREVENTION OR TREATMENT OF DIABETES

The invention refers to a synergistic pharmaceutical combination suitable for the prevention or treatment of a prediabetic state, metabolic X-syndrome or diabetes mellitus as well as disorders which are associated with the states listed above, namely endogenic metabolic disorders, insulin resistance, dislipidemia, alopecia, diffuse effluvium, polycystic ovary syndrome and/or other diabetic complications.

In the industrially developed countries more and more human being suffers from diabetes. The frequency of the disease is growing especially rapidly in the population above 50 of age. For example, the development of type 2 diabetes (i.e. non-insulin-dependent diabetes mellitus, NIDDM) is promoted by the defects in both the production and use of insulin. Genetic and environmental factors equally contribute to the formation of this wide-spread serious disease accompanied by significant mortality. The patient treated with insulin or another antidiabetic or anti-hyperlipidemic agent obtains, as a matter of fact, only a palliative treatment that improves the life quality, however, the complications which accompany the diabetes appear unavoidably. A significant part of the antidiabetic agents only enhances the production of insulin in the organism.

The aim of the invention is to provide a pharmaceutical combination which is suitable for the prevention of the development of diabetes or at least the complications that accompany diabetes, or, if such prevention is not possible anymore, for the efficient treatment of said complications.

It has been found that cicletanine [chemical name (±)-3-(4-chlorophenyl)-1,3-dihydro-6-methylfuro-[3,4-c]pyridin-7-ol], a known active agent having blood pressure lowering activity [US Patent No. 4,383,998], exerts an insulin sensitizing effect. For example, in cases when insulin is produced by the organism in a decreased amount, this available amount becomes sufficient to bring about the required physiological effect in the presence of cicletanine. Also in patients suffering from insulin resistance, the administration of cycletanine enhances the sensitivity of insulin. Consequently, a lower dosage of insulin or an antidiabetic or anti-hyperlipidemic active agent administered to the patient is sufficient to produce the therapeutical effect.

Thus, a first object of the invention is to provide a synergistic pharmaceutical combination suitable for the prevention or treatment of a prediabetic state, metabolic X-syndrome or diabetes mellitus as well as disorders which are associated with the states listed above, namely endogenic metabolic disorders, insulin resistance, dislipidemia, alopecia, diffuse effluvium, polycystic ovary syndrome and/or other diabetic complications.

A second object of the invention is to provide the use of cicletanine for the preparation of a pharmaceutical composition

having insulin sensitizing effect.

A third object of the invention is to provide a method for treating a patient suffering from or threatened by a prediabetic state, metabolic X-syndrome or diabetes mellitus as well as disorders which are associated with the states listed above, namely endogenic metabolic disorders, insulin resistance, dislipidemia, alopecia, diffuse effluvium, polycystic ovary syndrome and/or other diabetic complications with cicletanine.

The synergistic pharmaceutical combination of the invention comprises

(a) a first pharmaceutical composition containing cicletanine or a pharmaceutically suitable acid addition salt thereof and one or more conventional carrier(s), and

(b) a second pharmaceutical composition containing an antidiabetic or anti-hyperlipidemic active agent or, if desired and chemically possible, a pharmaceutically suitable acid addition salt or a salt formed with a pharmaceutically suitable base thereof and one or more conventional carrier(s).

Definition of expressions used in the description and claims

A pharmaceutical combination is an association of two pharmaceutically active agents in which

- either each of the active agents has been converted, one by one, to separate pharmaceutical compositions using one or more conventional carrier(s) and any of the usual processes of drug manufacture, and in this case the two sorts of

pharmaceutical composition obtained are administered to the patient simultaneously or one after the other following an interval; or

- the two active agents have been converted to one single pharmaceutical composition that can be administered to the patient being in need thereof. In the latter case, the pharmaceutical composition may contain a mixture of the two active agents, or each of the active agents may be present at a different site in the pharmaceutical composition, e.g. one of them in the tablet core and the other in a coating of the tablet core. Of course, one or more conventional carrier(s) and any of the usual processes of drug manufacture are used to prepare this single pharmaceutical composition.

Under an antidiabetic active agent (b_1) any of the pharmacologically active agents conventionally used in the therapy for the treatment of diabetes is meant. These are mainly the following:

- insulin,
- insulin sensitizing active agents,
- active agents that enhance the production of insulin,
- sulfonamides,
- biguanidine derivatives and
- α-glucosidase inhibitors.

As insulin, in the first place, human insulin prepared by recombinant technology is employed, which is administered, in general, parenterally.

The insulin sensitizing active agents enhance the effect of

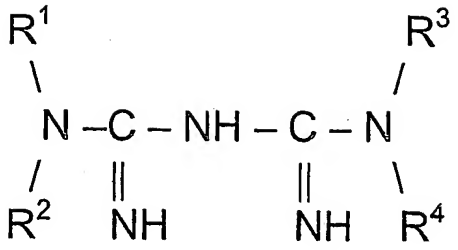
insulin. The most important sorts of them are the PPAR (peroxisome proliferator-activated receptor) γ-agonists, for example the thiazolidinedione derivatives such as pioglitazone [(±)-5-[[4-[2-(5-ethyl-2-pyridinyl)ethoxy]phenyl]methyl]-2,4-thiazolidinedione], troglitazone [(±)-5-[[4-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]-phenyl]methyl]-2,4-thiazolidinedione], ciglitazone [5-[[4-[(1-methylcyclohexyl)methoxy]phenyl]methyl]-2,4-thiazolidine-dione, rosiglitazone [(±)-5-[4-[2-[N-methyl-N-(2-pyridyl)amino]-ethoxy]benzyl]-2,4-thiazolidinedione] and other 2,4-thiazolidinedione derivatives as well as pharmaceutically suitable acid addition salts thereof.

The active agents that enhance the production of insulin are, for example, as follows: mitiglinide [(αS,3aR,7aS)-octahydro-γ-oxo-α-(phenylmethyl)-2H-isoindole-2-butanoic acid], repaglinide [(S)-2-ethoxy-4-[2-[[3-methyl-1-[2-(1-piperidinyl)phenyl]butyl]amino]-2-oxoethyl]benzoic acid], senaglinide (i.e. nateglinide) [N-[[(trans-4-(1-methylethyl)-cyclohexyl]carbonyl]-D-phenylalanine] or pharmaceutically suitable acid addition salts or pharmaceutically suitable salts thereof.

Out of the sulfonamides, the most important ones are the sulfonylurea derivatives e.g. tolbutamide [N-[(butylamino)-carbonyl]-4-methylbenzenesulfonamide], chlorpropamide [4-chloro-N-[(propylamino)carbonyl]benzenesulfonamide], tolazamide [N-[[(hexahydro-1H-azepin-1-yl)amino]carbonyl]-4-methylbenzenesulfonamide], acetohexamide [4-acetyl-N-

[(cyclohexylamino)carbonyl]benzenesulfonamide] etc. as first generation sulfonylureas or, for example, glyburide (glibenclamide) [5-chloro-N-[2-[4-[[[(cyclohexylamino)carbonyl]-amino]sulfonyl]phenyl]ethyl]-2-methoxybenzamide], glipizide [N-[2-[4-[[[(cyclohexyl-amino)carbonyl]amino]sulfonyl]phenyl]-ethyl]-5-methylpyrazine-carboxamide], gliclazide [N-[[(hexa-hydrocyclopenta[c]pyrrol-2(1H)-yl)amino]carbonyl]-4-methyl-benzenesulfonamide], glimepiride [trans-3-ethyl-2,5-dihydro-4-methyl-N-[2-[4-[[[[(4-methylcyclohexyl)amino]carbonyl]amino]-sulfonyl]phenyl]ethyl]-2-oxo-1H-pyrrole-1-carboxamide], gliquidone [N-[(cyclohexyl-amino)carbonyl]-4-[2-(3,4-dihydro-7-methoxy-4,4-dimethyl-1,3-dioxo-2(1H)-isoquinolinyl)ethyl]-benzenesulfonamide], glibornuride [N-[[(3-hydroxy-4,7,7-trimethylbicyclo[2.2.1]hept-2-yl)amino]carbonyl]-4-methyl-benzenesulfonamide], glisoxepid [N-[2-[4-[[[[(hexahydro-1H-azepin-1-yl)amino]carbonyl]amino]-sulfonyl]phenyl]ethyl]-5-methyl-3-isoxazolecarboxamide], glisentide [N-[2-[4-[[[(cyclo-pentylamino)-carbonyl]amino]sulfonyl]phenyl]-ethyl]-2-methoxybenzamide], glisolamide [N-[2-[4[[[(cyclohexyl-amino)carbonyl]amino]-sulfonyl]phenyl]ethyl]-5-methyl-3-isoxazolecarboxamide], glybuzole [N-[5-(1,1-dimethylethyl)-1,3,4-thiadiazol-2-yl]benzenesulfonamide], glyclopyramide [4-chloro-N-[(1-pyrrolidinylamino)carbonyl]benzenesulfonamide] etc. as second generation sulfonylureas and pharmaceutically suitable acid addition salts thereof.

The most important biguanidine derivatives can be characterized by the formula



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wherein

R^1, R^2, R^3 and R^4 represent, independently, a hydrogen atom, a C_{1-10} alkyl group, a naphthyl group, a phenyl group or a phenyl(C_{1-4} alkyl) group, wherein in both former cases the phenyl group is optionally substituted by 1-3 substituents which can be, independently, a halo atom, a C_{1-4} alkyl group or a C_{1-4} alkoxy group,

with the proviso that one of R^1, R^2, R^3 and R^4 is other than a hydrogen atom, or

R^1 and R^2 together with the adjacent nitrogen atom and/or R^3 and R^4 together with the adjacent nitrogen atom form a 5- or 6-membered, saturated, unsaturated or aromatic ring that can be fused with a further 5- or 6-membered saturated, unsaturated or aromatic ring optionally containing also a nitrogen atom,

and pharmaceutically suitable acid addition salts thereof.

Especially preferred biguanidine derivatives are metformin [N,N-dimethylimidocarbonimidic diamide], buformin [N-butylimidodicarbonimidic diamide] and phenformin [N-(2-phenylethyl)imidodicarbonimidic diamide].

The α-glucosidase inhibitors inhibit the enzyme α-glucosidase. Important representants thereof are, for example, miglitol [1,5-dideoxy-1,5-[(2-hydroxyethyl)imino]-D-glucitol], acarbose [O-4,6-dideoxy-4-[[[1S-(1α,4α,5β,6α)]-4,5,6-trihydroxy-(3-hydroxymethyl)-2-cyclohexen-1-yl]amino]-α-D-glucopyranosyl-(1→4)-O-α-D-glucopyranosyl-(1→4)-D-glucose], voglibose [3,4-dideoxy-4-[[2-hydroxy-1-(hydroxymethyl)ethyl]amino]-2-C-(hydroxymethyl)-D-epiinositol] etc.

Under an anti-hyperlipidemic active agent (b_2) any of the pharmacologically active agents conventionally used in the therapy for the treatment of high blood-lipid level is meant. These are compounds that can be classified mainly as follows:

aryloxyalkanoic acid derivatives,
HMG coenzyme reductase inhibitors,
nicotinic acid derivatives,
antacids for bile acids.

Out of the aryloxyalkanoic acid derivatives, preferred active agents are e.g. clofibrate [2-(4-chlorophenoxy)-2-methyl-propanoic acid ethyl ester], gemfibrozil [5-(2,5-dimethyl-phenoxy)-2,2-dimethylpentanoic acid], simfibrate [2-(4-chloro-phenoxy)-2-methylpropanoic acid 1,3-propanediyl ester], etofibrate [3-pyridinecarboxylic acid 2-[2-(4-chlorophenoxy)-2-methyl-1-oxopropoxy]ethyl ester], ciprofibrate [2-[4-(2,2-dichlorocyclopropyl)phenoxy]-2-methylpropanoic acid], ronifibrate [3-pyridinecarboxylic acid 3-[2-(4-chlorophenoxy)-2-methyl-1-oxopropoxy]propyl ester] etc.

Out of the HMG coenzyme reductase inhibitors, the most important active agents are the following: lovastatin [[1S-[1α(R*),3α,7β,8β(2S*,4S*),8αβ]]-2-methylbutanoic acid 1,2,3,7,8,8α-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester], fluvastatin [[R*,S*-(E)]-(±)-7-[3-(4-fluorophenyl)-1-(1-methyl-ethyl)-1H-indol-2-yl]-3,5-dihydroxy-6-heptenoic acid], pravastatin [[1S-[1α(βS*,δS*),2α,6α,8β(R*),8aα]]-1,2,6,7,8,8a-hexahydro-β,δ,6-trihydroxy-2-methyl-8-(2-methyl-1-oxobutoxy)-1-naphthaleneheptanoic acid monosodium salt], simvastatin [[1S-[1α,3α,7β,8β(2S*,4S*),8αβ]]-2,2-dimethylbutanoic acid 1,2,3,7,8,8a-hexahydro-3,7-dimethyl-8-[2-(tetrahydro-4-hydroxy-6-oxo-2H-pyran-2-yl)ethyl]-1-naphthalenyl ester], atorvastatin [[R-(R*,R*)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid] etc.

Out of the nicotinic acid derivatives, for example, the following ones are used: acipimox [5-methylpyrazinecarboxylic acid 4-oxide], niceritrol [3-pyridinecarboxylic acid 2,2-bis[[(3-pyridinylcarbonyl)oxy]methyl]-1,3-propanediyl ester], nicomol [3-pyridinecarboxylic acid (2-hydroxy-1,3-cyclohexane-diylidene)-tetrakis(methylene) ester], nicoclonate [3-pyridine-carboxylic acid 1-(4-chlorophenyl)-2-methylpropyl ester] etc.

Out of the antacids that bind the bile acids, important ones are the following: colestipol [a basic anion exchange resin: N-(2-aminoethyl)-N'-[2-[(2-aminoethyl)amino]-ethyl]-1,2-ethane-diamine polymer with (chloromethyl)oxirane], cholestyramine [a

synthetic, strongly basic anion exchange resin containing quaternary ammonium functional groups which are attached to a styrene-divinylbenzene copolymer], polidexide [an anion exchange resin containing quaternary ammonium groups which bind the bile acids in the intestine] etc.

The antidiabetic and anti-hyperlipidemic active agents are known from the literature. If desired and chemically possible, these active agents can be used in the form of the pharmaceutically suitable acid addition salts thereof or in the form of the salts formed with pharmaceutically suitable bases.

Under a pharmaceutically suitable acid addition salt, an acid addition salt formed with a pharmaceutically suitable inorganic acid such as hydrogen chloride or sulfuric acid and the like, or with a pharmaceutically suitable organic acid such as acetic acid, fumaric acid, lactic acid and the like is meant.

When the antidiabetic or anti-hyperlipidemic active agent has a chemical structure that can form a salt with a base, also the salt of the active agent formed with a pharmaceutically suitable inorganic or organic base can be used. When said active agent can form an acid addition salt with an acid, a pharmaceutically suitable acid addition salt of the active agent can be employed, too.

In formula I, the C_{1-4} alkyl group can be a methyl, ethyl, n-propyl, isopropyl, n-butyl, sec,-butyl, tert.-butyl, or isobutyl group. The C_{1-10} alkyl group may be, in addition to the ones listed above, for example, a pentyl, hexyl, heptyl, octyl, nonyl or decyl group, too. A C_{1-4} alkoxy group can be, for example, a

methoxy, ethoxy, n-propoxy or n-butoxy group. A halo atom is, for example, a fluoro, chloro, bromo or iodo atom. A 5- or 6-membered, saturated, unsaturated or aromatic ring containing a nitrogen atom is, for example, a pyrrole, isopyrrole, dihydro-pyrrole, pyrrolidine, pyridine, piperidine, dihydropyridine, tetra-hydropyridine ring or the like.

In the synergistic pharmaceutical combination of the invention, the mass (or weight) ratio of the cicletanine or a pharmaceutically suitable acid addition salt thereof and the antidiabetic or anti-hyperlipidemic active agent or, if desired and chemically possible, a pharmaceutically suitable acid addition salt or a salt formed with a pharmaceutically suitable base thereof is, in general, (1-100):(100-1). In general, the one or two pharmaceutical composition(s) of the pharmaceutical combination is/are suitable for peroral or parenteral administration and is/are solid or liquid composition(s). The suitable dosage forms and manufacture thereof as well as the useful carriers are known from the literature e.g. Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, USA.

In the synergistic pharmaceutical combination of the invention, each active agent can be present in a separate pharmaceutical composition or both cicletanine and the antidiabetic or anti-hyperlipidemic active agent are present in a single common pharmaceutical composition. The antidiabetic or anti-hyperlipidemic active agent can be, for example, one of the species listed above. Thus, the preferred synergistic pharmaceutical combination of the invention may contain

cicletanine or a pharmaceutically suitable acid addition salt thereof such as the hydrochloride as well as (b_1) an anti-diabetic active agent e.g. insulin, or an insulin sensitizing active agent such as a thiazolidinedione derivative, for example, pioglitazone, troglitazone, ciglitazone, rosiglitazone, or an active agent that enhances the production of insulin such as mitiglinide, repaglinide, senaglinide, or a sulfonamide such as tolbutamide, chlorpropamide, tolazamide, acetohexamide, glyburide, glipizide, gliclazide, glimepiride, gliquidone, glibornuride, glisoxepid, glisentide, glisolamide, glybuzole, glyclopyramide, or a biguanidine derivative of the formula I, preferably metformin, buformin, phenformin, or an α-glucosidase inhibitor such as miglitol, acarbose or voglibose, or (b_2) an anti-hyperlipidemic active agent e.g. an aryloxyalkanoic acid derivative such as clofibrate, gemfibrozil, simfibrate, etofibrate, ciprofibrate, ronifibrate, or a HMG coenzyme reductase inhibitor such as lovastatin, fluvastatin, pravastatin, simvastatin, atorvastatin, or a nicotinic acid derivative such as acipimox, niceritrol, nicomol, nicoclonate, or an antacid for bile acids such as colestipol, cholestyramine, polidexide, or, if desired and chemically possible, a pharmaceutically suitable acid addition salt or a salt formed with a pharmaceutically suitable base of the species given under (b_1) and (b_2).

The influence of the combination of the invention on the glucose sensitivity was studied using the following tests. All experiments performed conform to the European Community guiding principles for the care and use of experimental

animals.

Adult male New Zealand white rabbits weighing 3-3.2 kg, housed in an animal room (12-hour light/dark periods a day, temperature of 22-25 °C, relative humidity of 50-70 %) with one animal per pen, fed commercial laboratory chow and tap water ad libitum, were used throughout. The animals underwent surgery after a two-week adaptation period [Szilvassy Z. et al., Br. J. Pharmacol., 112, 999-1001 (1994)].

Surgery was performed under aseptic conditions. The rabbits were anaesthetized with an intravenous bolus of 10 mg/kg diazepam (Sigma, St. Louis, MO, USA) and 5 mg/kg ketamine (EGIS Pharmaceuticals Ltd., Budapest, Hungary). Lidocaine (EGIS Pharmaceuticals Ltd., Budapest, Hungary) was administered subcutaneously for local pain relief. Polyethylene catheters were inserted into two major branches of the jugular vein and the left carotid artery. The catheters were exteriorised through the back of the neck. These lines were kept patent by filling with sodium heparin solution (100 IU/ml).

Human regular insulin was infused at a constant rate (13 mU/kg, NOVO Nordisk, Copenhagen) via one of the venous catheters over 120 min. This insulin infusion yielded plasma insulin immunoreactivity of 100±5 μU/ml in the steady state. This value corresponds to five times the value of the normal upper limit. Blood samples (0.3 ml) were taken from the arterial cannula for blood glucose concentration at 10 min intervals. Blood glucose concentration was maintained constant (5.5±0.5 mmol/litre) by a variable rate of glucose infusion via the second

venous cannula. When blood glucose had stabilized for at least 30 min, we defined this condition as steady state. In the steady state, additional blood samples (0.5 ml) were taken for plasma insulin determination at 10-min intervals. The glucose infusion rate (mg/kg/min) during steady state was used to characterize insulin sensitivity [DeFronzo R.A. et al., Am. J. Of Physiol., 237, E214-223 (1979)]. The test compound(s) was/were administered to healthy and hypercholesterolaemic animals, respectively, perorally, in a single dose, daily, for five days, and the glucose infusion rates determined on the 6th day were averaged within each test group consisting of 6 animals. One group of the healthy and one of the hypercholesterolaemic animals was used as the control. The results obtained are shown in Tables 1, 2, and 3.

Table 1

Insulin sensitivity as characterized by the glucose infusion rate in mg/kg/min during steady state

Group of animals	**Control**	**Cicletanine** (30 mg/kg) p.o.	**Metformin** (100 mg/kg) p.o.	**Cicletanine** (30 mg/kg) + **metformin** (100 mg/kg) p.o.
normal	13,8±1,11	16,2±1,35	14,4±1,03	19,4±1,32
HC	7,9±1,3	14,2±1,31	10,7±1,01	15,6±1,12

normal = healthy animals were used in the test;

HC = hypercholesterolaemic animals were used in the test.

Table 2

Insulin sensitivity as characterized by the glucose infusion rate in mg/kg/min during steady state

Group of animals	**Control**	**Cicletanine** (30 mg/kg) p.o.	**Troglitazone** (75 mg/kg) p.o.	**Cicletanine** (30 mg/kg) + **troglitazone** (75 mg/kg) p.o.
normal	13,2±0,98	16,9±1,13	14,3±0,08	19,8±2,00
HC	8,2±0,76	13,5±1,41	13,2±1,06	15,7±0,99

normal = healthy animals were used in the test;

HC = hypercholesterolaemic animals were used in the test.

Table 3

Insulin sensitivity as characterized by the glucose infusion rate in mg/kg/min during steady state

Group of animals	Control	Cicletanine (30 mg/kg) p.o.	Glyburide (1 mg/kg) p.o.	Cicletanine (30 mg/kg) + glyburide (1 mg/kg) p.o.
normal	13,44±0,86	15,9±0,89	11,8±1,38	16,4±2,22
HC	8,4±1,09	12,9±1,06	7,0±1,00	14,91±0,78

normal = healthy animals were used in the test;
HC = hypercholesterolaemic animals were used in the test.

As a matter of fact, the amount of glucose infused to obtain constant blood glucose level has been measured in the above tests. It is favourable that a higher amount of glucose should be needed at the given constant blood glucose level which indicates the enhanced effect of insulin. Consequently, the higher glucose infusion rate is measured, the higher efficiency is obtained with the compound tested.

As seen in Table 1, in healthy animals, of course, higher values are obtained than in hypercholesterolaemic ones. In the control groups, lower glucose infusion rates are experienced than in the groups treated with either cicletanine or metformin. Anyway, in both healthy and cholesterolaemic animals, the glucose infusion rates are significantly higher when the animals has been treated with both cicletanine and metformin than in the case when only one of the test compounds has been

administered. Thus, synergism is observed between cicletanine and metformin.

The situation is the same with cicletanine and troglitazone as well as cicletanine and glyburide as shown by Table 2 and Table 3, respectively.

Thus, the especially preferred synergistic pharmaceutical combination of the invention contains (a) cicletanine or a pharmaceutically suitable acid addition salt thereof and (b) a biguanidine derivative of the formula I, suitably metformin, or a pharmaceutically suitable acid addition salt thereof, or a sulfonylurea, suitably glyburide, or a pharmaceutically suitable acid addition salt thereof, or a thiazolidinedione derivative, suitably troglitazone, or a pharmaceutically suitable acid addition salt thereof, wherein the active agents are present in separate pharmaceutical compositions or in a single pharmaceutical composition.

The invention includes also the use of cicletanine or a pharmaceutically suitable acid addition salt thereof for the preparation of a pharmaceutical composition having insulin sensitizing effect. Preferably, the pharmaceutical composition is a unit dosage form, in general, suitable for peroral or parenteral administration, and contains 30 to 100 mg of cicletanine or cicletanine hydrochloride. The suitable dosage forms and manufacture thereof as well as the useful carriers are known from the literature e.g. Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, USA.

The insulin sensitizing effect of various doses of cicletanine

was studied using similar tests employed in the study of glucose sensitivity of the synergistic pharmaceutical combination of the invention. The animals were treated with 10 mg/kg, 30 mg/kg or 100 mg/kg of cicletanine, perorally, once daily, for 5 days. The glucose infusion rate was determined on the 6th day. The results obtained are shown in Table 4.

Table 4

Insulin sensitivity as characterized by the glucose infusion rate in mg/kg/min during steady state

Group of animals	Control	Cicletanine (10 mg/kg) p.o.	Cicletanine (30 mg/kg) p.o.	Cicletanine (100 mg/kg) p.o.
normal	13,44±0,86	14,9±1,11	16,8±1,52	15,9±0,83
HC	8,4±1,09	11,2±1,21	13,5±1,41	14,26±1,16

normal = healthy animals were used in the test;
HC = hypercholesterolaemic animals were used in the test.

As a matter of fact, in the latter test the influence of various doses of cicletanine on the utilization of insulin produced by the pancreas was studied. From tha data of Table 4 it can be seen that, relative to the control group, even a peroral dosage of as low as 10 mg/kg of cicletanine enhances the utilization of insulin produced by the organism in both healthy and hyper-cholesterolaemic animals. (The control data indicate the

amount of glucose to be administered by infusion which amount is required to produce an euglycaemic state in hyperinsulinaemic animals.) Of course, the higher doses of cicletanine produced still favourable utilizations of insulin.

The invention includes also a method for the treatment or the prevention of a prediabetic state, metabolic X-syndrome or diabetes mellitus as well as disorders which are associated with the states listed above, namely endogenic metabolic disorders, insulin resistance, dislipidemia, alopecia, diffuse effluvium, polycystic ovary syndrome and/or other diabetic complications, in which the patient suffering from or threatened by said states is treated with a therapeutically effective amount of cicletanine or a pharmaceutically suitable acid addition salt thereof. The therapeutically effective amount of cicletanine is an amount that produces insulin sensitizing effect.

In addition to cicletanine or a pharmaceutically suitable acid addition salt thereof, if desired, also an antidiabetic or anti-hyperlipidaemic active agent can be administered to the patient suffering from or threatened by the states listed above. In this case the antidiabetic or anti-hyperlipidemic active agent and the cicletanine or a pharmaceutically suitable acid addition salt thereof can be administered simultaneously or one after the other following a shorter interval lasting for e.g. some seconds or minutes or a longer interval lasting for e.g. 10-30 minutes.

Since the cicletanine synergistically enhances the therapeutical effect of the antidiabetic or anti-hyperlipidemic active agent, the daily dose of the antidiabetic or anti-

hyperlipidemic agent is lower than the usual daily dose thereof employed in the conventional treatment when no cicletanine is administered.

The daily dose of cicletanine is, in general 30 to 100 mg, preferably about 50 mg for an adult person having a body weight of 70 kg.

Using the process of the invention, the development of especially the following clinical patterns can be prevented, or, when once developed, they can be influenced advantageously:

- prediabetic state such as glucose intolerance or insulin resistance,
- metabolic X-syndrome,
- both types of diabetes (IDDM and NIDDM),
- diabetic complications with special regards to retinopathy, neuropathy, nephropathy, polycystic ovary syndrome (PCOS), alopecia, diffuse effluvium, gestation diabetes mellitus (GDM), arterial hypertonia, dislipidemia, arterio-sclerosis, obesitas, cardial ischemia associated with diabetes etc.

Thus, a pharmaceutical composition containing cicletanine or a pharmaceutically suitable acid addition salt thereof can be administered to a patient that is treated or conventionally should be treated with an antidiabetic or anti-hyperlipidemic active agent in order to prevent or treat a prediabetic state, metabolic X-syndrome or diabetes mellitus as well as disorders which are associated with the states listed above, namely endogenic metabolic disorders, insulin resistance, dislipidemia,

alopecia, diffuse effluvium, polycystic ovary syndrome and/or other diabetic complications. As a result of the administration of the pharmaceutical composition containing cicletanine or a pharmaceutically suitable acid addition salt thereof, either no further treatment with an antidiabetic or anti-hyperlipidemic active agent is required, or a lower dosage of the antidiabetic or anti-hyperlipidemic active agent is sufficient. When a pharmaceutical composition containing cicletanine or a pharmaceutically suitable acid addition salt thereof as the active agent is administered to a patient suffering from diabetes and obtaining a regular insulin treatment, then the daily insulin dose can be reduced, thus, avoiding the development of insulin resistance.

Claims:

1. A synergistic pharmaceutical combination suitable for the prevention or treatment of a prediabetic state, metabolic X-syndrome or diabetes mellitus as well as disorders which are associated with the states listed above, namely endogenic metabolic disorders, insulin resistance, dislipidemia, alopecia, diffuse effluvium, polycystic ovary syndrome and/or other diabetic complications comprising

(a) a first pharmaceutical composition containing cicletanine or a pharmaceutically suitable acid addition salt thereof and one or more conventional carrier(s), and

(b) a second pharmaceutical composition containing an antidiabetic or anti-hyperlipidemic active agent or, if desired and chemically possible, a pharmaceutically suitable acid addition salt or a salt formed with a pharmaceutically suitable base thereof and one or more conventional carrier(s).

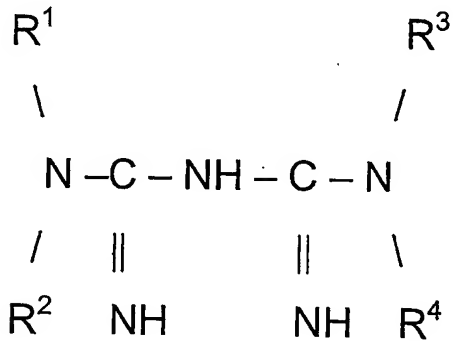
2. A pharmaceutical combination of Claim 1 in which a single pharmaceutical composition comprises both the cicletanine or a pharmaceutically suitable acid addition salt thereof and the antidiabetic or anti-hyperlipidemic active agent or, if desired and chemically possible, a pharmaceutically suitable acid addition salt or a salt formed with a pharmaceutically suitable base thereof.

3. A pharmaceutical combination of Claim 1 or 2 comprising a thiazolidinedione derivative or a pharmaceutically suitable acid addition salt thereof as the antidiabetic active agent.

4. A pharmaceutical combination of Claim 1 or 2 comprising

a sulfonylurea or a pharmaceutically suitable acid addition salt thereof as the antidiabetic active agent.

5. A pharmaceutical combination of Claim 1 or 2 comprising a biguanidine derivative of the formula I, wherein



I

wherein

R^1, R^2, R^3 and R^4 represent, independently, a hydrogen atom, a C_{1-10} alkyl group, a naphthyl group, a phenyl group or a phenyl(C_{1-4} alkyl) group, wherein in both former cases the phenyl group is optionally substituted by 1-3 substituents which can be, independently, a halo atom, a C_{1-4} alkyl group or a C_{1-4} alkoxy group,

with the proviso that one of R^1, R^2, R^3 and R^4 is other than a hydrogen atom, or

R^1 and R^2 together with the adjacent nitrogen atom and/or R^3 and R^4 together with the adjacent nitrogen atom form a 5- or 6-membered, saturated, unsaturated or aromatic ring that can be fused with a further 5- or 6-membered saturated,

unsaturated or aromatic ring optionally containing also a nitrogen atom,

or a pharmaceutically suitable acid addition salt thereof as the antidiabetic active agent.

6. A pharmaceutical combitanion of Claim 5 comprising metformin or a pharmaceutically suitable acid addition salt thereof as the antidiabetic active agent.

7. A pharmaceutical combination of Claim 1 or 2 comprising insulin, pioglitazone, troglitazone, ciglitazone, rosiglitazone, mitiglinide, repaglinide, senaglinide, tolbutamide, chlorpropamide, tolazamide, acetohexamide, glyburide, glipizide, gliclazide, glimepiride, gliquidone, glibornuride, glisoxepid, glibenclamide, glisentide, glisolamide, glybuzole, glyclopyramide, metformin, buformin, phenformin, miglitol, acarbose or voglibose, clofibrate, gemfibrozil, simfibrate, etofibrate, ciprofibrate, ronifibrate, lovastatin, fluvastatin, pravastatin, simvastatin, atorvastatin, acipimox, niceritrol, nicomol, nicoclonate, colestipol, cholestyramine, polidexide or, if desired and chemically possible, a pharmaceutically suitable acid addition salt or a salt formed with a pharmaceutically suitable base thereof as the antidiabetic or anti-hyperlipidemic active agent.

8. Use of cicletanine or a pharmaceutically suitable acid addition salt thereof for the preparation of a pharmaceutical composition having insulin sensitizing effect.

9. The use of Claim 5 in which each pharmaceutical composition contains 30 to 100 mg of cicletanine or cicletanine

hydrochloride.

10. A method for the treatment or the prevention of a prediabetic state, metabolic X-syndrome or diabetes mellitus as well as disorders which are associated with the states listed above, namely endogenic metabolic disorders, insulin resistance, dislipidemia, alopecia, diffuse effluvium, polycystic ovary syndrome and/or other diabetic complications, in which the patient suffering from or threatened by said states is treated with a therapeutically effective amount of cicletanine or a pharmaceutically suitable acid addition salt thereof.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/HU2004/000037

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/4355 A61K31/155 A61K31/427 A61K31/64 A61P3/00
A61P3/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BIOSIS, EMBASE, CHEM ABS Data, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DURAN M J ET AL: "Protective effect of cicletanine on renal function in uninephrectomized diabetic spontaneously hypertensive rats" EUROPEAN HEART JOURNAL, vol. 20, no. ABSTR. SUPPL., August 1999 (1999-08), page 422, XP009035503 & XXIST CONGRESS OF THE EUROPEAN SOCIETY OF CARDIOLOGY; BARCELONA, SPAIN; AUGUST 28-SEPTEMBER 1, 1999 ISSN: 0195-668X abstract	10

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"P" document published prior to the international filing date but later than the priority date claimed

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 August 2004	06/09/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Ansaldo, M

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	US 4 383 998 A (ESANU ANDRE) 17 May 1983 (1983-05-17) column 5, line 67 - column 6, line 1; claims 1,2; example 5	10

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